Barriers to HAART Adherence Among Human Immunodeficiency Virus–Infected Adolescents

Debra A. Murphy, PhD; Moussa Sarr, MD, MPH; Stephen J. Durako; Anna-Barbara Moscicki, MD; Craig M. Wilson, MD; Larry R. Muenz, PhD; for the Adolescent Medicine HIV/AIDS Research Network

Objectives: To investigate the barriers to highly active antiretroviral therapy (HAART) adherence among human immunodeficiency virus (HIV)–infected adolescents and to explore the association of barriers and nonadherence.

Design: Structured interviews were conducted to determine the barriers associated with adherence; principal component factor analysis was performed on scores of the 19 barrier variables.

Setting: Human immunodeficiency virus–infected adolescents were recruited from 13 US cities into the REACH (Reaching for Excellence in Adolescent Care and Health) Project, the first large-scale disease progression study of HIV-positive adolescents infected through sexual behavior such as this is extremely difficult for a patient’s health-related behaviors correspond with medical advice. Current recommendations for antiretroviral therapy use in HIV-infected persons from the International AIDS Society–USA Panel include continuous assessment of adherence, with at least 95.0% adherence needed for best results in therapy. Almost perfect adherence such as this is extremely difficult for patients prescribed complex antiretroviral regimens. One study in 2000 reported that antiretroviral regimens contained on average 14.7 capsules or pills per day for HIV-infected adults with up to 36 doses per day prescribed for some patients. Moreover, some of the medications require patients to follow special instructions (eg, fasting or taking...
ing antiretroviral drugs with high-fat meals); adverse effects are common. However, there is research to show that even modest or occasional nonadherence to HAART can significantly decrease treatment benefits.\textsuperscript{10,11} Patients, therefore, face many obstacles in adhering to these complicated treatment regimens. While much research is being conducted to judge whether structured intermittent treatments can reduce adverse effects and costs as well as improving both adherence and prognosis, it is still thought essential that adherence to a potentially modified therapeutic regimen be maximized.\textsuperscript{12} Also, failure to adhere permits the virus to resume its typical rapid replication—as many as 10\textsuperscript{10} viral particles produced per day.\textsuperscript{13,14} which allows the generation of resistant mutant strains that are no longer responsive to available antiretroviral drugs, posing clear public health implications.\textsuperscript{15}

The barriers or obstacles that patients perceive as affecting their antiretroviral adherence have been investigated among adults in many studies. In a recent study, common reasons associated with nonadherence were sleeping through dose time, problems in following special instructions, and changes in daily routines.\textsuperscript{9} In another study of HIV-infected adults, the most frequent reasons for nonadherence reflected general concerns about treatment, as a reminder of one's HIV status, not wanting other people to know one's HIV status, and difficulty remembering to ask health care providers questions about treatment.\textsuperscript{16} Such perceived barriers have been found to be associated with adherence: in a sample of 158 HIV-infected adults, there was a 6.0% increase in risk of being nonadherent for every point increase in barrier score.\textsuperscript{17}

There has long been evidence that factors directly related to medication regimens can be barriers to adherence. A linear decrease in adherence with increasing number of doses per day has been verified across a number of studies of adults with other illnesses.\textsuperscript{18} The number of medications prescribed also has been found to affect adherence.\textsuperscript{19,20} However, in addition to barriers directly related to regimens, patient perceptions of whether the medications will actually benefit them substantially seem to be a potentially significant barrier. Patient acceptance of therapy has been found to be associated with trust in the medications’ efficacy and safety among adult women.\textsuperscript{21}

Cultural background and environment may also influence reasons for adherence. Freeman et al\textsuperscript{17} reported statistically significant barrier differences by race, with whites more likely to report that medications were inconvenient, and that they were taking more medication than desired. African Americans were more likely to report they had no storage place for medications, they ceased medications when they felt better, they did not take medications when away from home, and they were embarrassed to get refills. These investigators reported that 2 barriers differed by sex, with women reporting they were more likely than men to forget to refill medications and to not understand how to take the medications. Among Latinos, the most frequently reported barriers were feeling depressed or overwhelmed, simply forgetting, and sleeping through a dose.\textsuperscript{22}

Most research conducted in this area has been done with adults. To our knowledge, only 2 studies thus far have examined adherence among HIV-infected adolescents. Among the REACH (Reaching for Excellence in Adolescents' Care and Health) Project HIV-infected adolescent cohort\textsuperscript{23} significant nonadherence was found among the HIV-infected adolescents with only 41.0% reporting consistent adherence to their HAART regimen. Variables associated with nonadherence were as follows: there was a trend for an inverse association between the number of drugs prescribed and adherence, with more drugs associated with lower adherence. In addition, depression was significantly associated with decreased adherence. In the second study conducted with HIV-infected adolescents, Belzer et al\textsuperscript{24} found that having too many pills to take was the most commonly reported reason for missing medications, and adolescents who believe that their medication would improve the quality of their lives were more likely to have 90.0% or more adherence.

The overall objective of this study was to conduct an in-depth investigation of the barriers to HAART adherence among HIV-infected adolescents and to explore the association of barriers and nonadherence. Specific aims include (1) to investigate the main barriers to antiretroviral regimen adherence among HIV-infected adolescents in the REACH Project cohort; (2) to explore the association of barriers and nonadherence; (3) to determine the current level of adolescent adherence; and (4) to explore the relationship between the level of adherence and factors that may be associated with adherence.
required parental permission for participation of youth in this study while others did not; local requirements were followed at each site.

Data used in this analysis were obtained from 3 sources—direct face-to-face interview, laboratory analysis, and medical record review. The specific questions that were used for this analysis were asked as part of a more extensive face-to-face interview regarding the subject’s recent medical history. Clinical site personnel were initially centrally trained to administer the face-to-face interviews; the interviewers were all nurses or nurse practitioners. The medication adherence assessment and subject characteristics were obtained in the face-to-face interview since adolescents are often unsure of the names of their medications and need to describe them, and they often have difficulty reading the complicated medication names. Medical record abstraction was used to determine the medications prescribed.

**ASSESSMENT MEASURES**

**Laboratory Measures**

There are 2 laboratory evaluations used in this report. Quantitative immunophenotyping of CD4+ T-cell lymphocyte counts were determined at the individual clinical sites in certified laboratories using AIDS Clinical Trials Group standardized flow cytometry protocols. Human immunodeficiency virus 1 RNA level in plasma was measured in a centralized laboratory on frozen specimens using either nucleic acid sequence–based amplification or NucliSens assays (Organon Teknika, Durham, NC).26 The respective lower limits of detection for the nucleic acid sequence–based amplification and NucliSens assays were 400 and 80 copies/mL, respectively.

**Adherence Measures**

Self-report adherence data were collected by direct face-to-face interview as previously reported.21 Prescribed antiretroviral medications were transcribed from the medical records. Before subject visits, the study coordinator reviewed patient medical records to determine what medications were prescribed, when taking the medications was initiated and stopped, and what the dosage was. At the study visit, subjects were asked questions to identify both the medication and regimen as well as questions regarding adherence over the last month, last 2 days, and the last weekend, based on the Adult AIDS Clinical Trials Group Adherence Baseline Questionnaire.27

If the subject reported anything other than complete adherence over the past month, he or she was asked questions related to reasons for not taking the prescribed medications (Figure). Subjects were given a list of 19 potential reasons for missing their medication as well as an opportunity to mention other reasons not on the list. For each particular reason for non-adherence, the subjects were asked how often this reason applied to them in the last month using a 4-point Likert scale (1 indicates never; 2, rarely; 3, sometimes; and 4, often). Twelve of the 19 questions (items 1-3, and 5-13 in Table 1) were from the Adult AIDS Clinical Trials Group Adherence Instruments.28 In some cases minor wording changes were made to make the items more understandable to adolescents. The remaining 7 questions were developed by us, based on adolescent-specific issues (item 4 and items 14-19; Table 1).

**STATISTICAL ANALYSIS**

All statistical tests were performed using SAS version 8.1 software (SAS Institute Inc, Cary, NC). We generated means and simple proportions as appropriate to describe the study population. For descriptive purposes, we also computed the frequencies and proportions of the 19 “barrier of adherence” variables. A score of 0 was assigned to each of the barriers when patients reported that the item was “never” a reason for non-adherence. If the patients response was “rarely,” “sometimes,” or “often,” the assigned scores to the barriers were 1, 2, and 3, respectively.

Principal component factor analysis29,30 was performed on scores of the 19 barrier variables. The initial factor solutions were followed with a variance maximization (Varimax-rotated; Varimax Information Systems Inc, Saskatoon, Saskatchewan) solution to facilitate their interpretation. All of the analyses were performed cross-sectionally using the first available visit after the
CHARACTERISTICS OF THE STUDY SAMPLE

The questions concerning barriers to medication adherence were added to the face-to-face interview in July 1998 and were asked only if the subject was HIV positive, had been prescribed HAART, and acknowledged problems with adherence in the last month. At the time of this analysis, 550 adolescents were participating in the REACH Project. We excluded 197 of them who were HIV negative, and 194 HIV-positive subjects were not receiving HAART. Among the 159 youth taking HAART, 71.7% (n=114) reported missing at least 1 dose over the previous month, while 28.3% (n=45) reported full adherence. The results and discussions about how nonadherent adolescents compare with the adherent adolescents in the REACH Project population are published elsewhere.31 Only the 114 subjects with incomplete medication adherence data were included in the present study since they were the ones responding to the barriers to adherence questions. Consistent with the remainder of the REACH Project sample,31 most subjects were female (73.0%) and African American (72.0%). Female subjects were not more likely to be prescribed HAART or to be nonadherent than male subjects. Twenty-five percent of the female subjects were nonadherent vs 22.5% of the male subjects (P= .73); 45.6% of the female subjects were prescribed HAART vs 50% of the male subjects (P = .48; data not shown). A detailed description of the national REACH Project study design, methods, and population can be found in Wilson et al31 (Table 2).

Viral load should be associated with adherence to HAART; therefore, the adherence measure was validated by comparison with HIV viral load, and a significant association was found. We found viral load measures 10 000 copies/mL or more in 22.2% of those who never missed a medication vs 44.3% of those who did miss a medication in the past month (P = .02).

DESCRIPTION OF THE BARRIERS TO ADHERENCE

The 3 most commonly endorsed reasons for nonadherence to HAART, combining the sometimes and often responses were simply forgot (45.6%), did not have medication with them (42.1%), and change in daily routine (33.3%) (Figure). Fewer than 10.0% of adolescents reported the following reasons for nonadherence: confused about when/to take drug(s) (5.3%), “felt like drug was toxic/harmful” (7.9%), and “felt like meds had no positive effect” (9.6%).

No reason was cited as often relevant by more than 20.0% of respondents. However, simply forgot and did not have medication with them were cited by more than 40.0% of respondents as at least sometimes relevant to their nonadherence. Ten more reasons were cited by 20.0% to 40.0% of the respondents as relevant at least sometimes. Four of 7 items that were at most rarely endorsed refer to the drugs’ medical efficacy and safety (ie, such considerations were rarely cited as reasons).
BARRIERS TO ADHERENCE FACTOR ANALYSIS

A factor analysis, using principal component factor analysis was applied to these data, using scores of 1 through 4 to assign a number to each response. The analysis yielded 6 factors with eigenvalues greater than 1, accounting for 68.1% of the total variance. The first 2 factors yielded eigenvalues greater than 2 and the variance dropped greatly from factor 2 (10.8) to factor 3 (07.7) and subsequent factors. We, therefore, chose to report a 2-factor model accounting for 42.6% of the variance.

The component loadings of the 2 factors after a Varimax-rotated solution are provided in Table 1. The first factor, accounting for the largest proportion of the variance, 31.8%, had 11 substantial loadings (items that loaded above 0.50 on each factor). These items dealt with objective and subjective perceptions toward the drugs, including adverse effects, toxic effects, and efficacy. They also included items related to social and psychological influence toward the drugs (“did not want others to notice medication,” “reminder that you have HIV”) and symptoms (“felt healthy, so didn’t take it” or “felt depressed or overwhelmed”).

The second factor accounted for 10.8% of the variance and it had 5 substantial loadings. In all these items, the focus was on attitudes toward interactions between lifestyle and treatment regimen (“busy with other things,” “simply forgot,” “change in daily routine,” “slept through dose time,” and “already missed meds—blew it for the day”). Subsequent bivariate analysis once the factor analysis was done did not show significant differences by age, sex, or race (data not shown).

Adherence to antiretroviral medications reported in this sample is poor. Only 28.3% of adolescents reported taking all of their prescribed antiretroviral medications in the previous month. This adherence rate is lower than that reported for HIV-infected adult males and for HIV-infected mothers with a young child. Health and psychosocial service providers who worked in the area of HIV-AIDS care in the early stages of the epidemic remember a time when almost all patients eventually died a few years after having been diagnosed as having AIDS. Tremendous advances in the treatment of HIV through therapeutic medication regimens to control the virus have been made since then. But these advances are only effective if patients adhere to the medication regimens, and in this sample 72.0% of the adolescents reported not taking all their medication in the previous month. This is particularly worrisome, as we do not yet know the long-term consequences of developing resistance to a number of therapeutic regimens, what new antiretroviral medications may or may not be developed in the future, and whether these adolescents face a lifetime of taking antiretroviral medications as their disease progresses.

One potential limitation of this study is that adherence was measured by self-report. However, adolescent self-report of medication compliance has been found to be reasonably accurate. Most adolescent females reporting on contraceptive compliance were found to have described themselves accurately in terms of compliance behavior. Adolescents are not only willing to openly report noncompliance, but will specify the type of noncompliance: undermedication, cyclical noncompliance, or overmedication. Rates of adolescent medication noncompliance reported in studies using laboratory assay are consistent with rates reported in studies using self-report. In the REACH Project cohort, we have investigated the accuracy of self-report of marijuana in a comparison of self-report data to urinalysis. The level of self-report among the HIV-infected adolescents was exceptionally high.

Previous studies indicate that adherence in patients with chronic illness can be influenced by programs that work to improve organizational skills. Many schools have adapted relatively intense programs lasting from 1 full day to 1 week that work with new incoming students to orient them to classroom schedules. Diabetic programs offer similar intensive programs that include organizational skills and working with daily schedules. These type of classes occur over 8- to 12-week periods. However, adolescent medicine programs toward medication adherence in HIV-infected adolescents rarely commit to this much time. Our data support that adherence is tied closely with daily routine in many individuals. When schedules are disrupted adherence becomes difficult. These findings support the notion that working closely with adolescents to improve organizational skills may be helpful in improving adherence.

As noted, forgetting to take the medications and changes in daily routine were 2 of the main barriers cited by respondents as reasons for nonadherence. These are similar to reports of barriers to adherence by both English-speaking and Spanish-speaking adults. Adolescents who do not tie in taking their medications with regular daily activities have difficulty sticking to their treatment regimen. Especially among adolescents, it is possible that adherence should be viewed as more than a problem of taking medication—that it may entail certain lifestyle changes to accommodate the treatment regimen. This observation is consistent with prior research on health behaviors such as smoking cessation, in which changing environmental factors can assist in breaking maladaptive behavior chains, and has been shown to be an important factor in achieving the desired behavioral goals.

Simplified medication regimens may also improve adherence in adolescents. Pharmaceutical companies have begun marketing medications that are easier to take. Unfortunately, as patients become increasingly experienced with different antiretroviral medications (ie, they have taken more medications in the past), their regimens typically also become more complicated with more pills and more complicated medication schedules. Assisting HIV-infected adolescents to develop strategies to take their medications as prescribed and simplifying medication regimens early in treatment may be important in setting the stage for long-term adherence.

Factor analysis of the barriers to adherence scale indicates there are 2 main factors accounting for the largest proportion of the variance. These can best be described as (1) medication-related adverse effects, both physical and psychological and (2) complications in day-
What This Study Adds

Only 2 studies have been conducted investigating antiretroviral adherence among HIV-infected adolescents,23,24 and one of those was the preliminary baseline data from this REACH Project cohort.21 The first study only focused on rates of adherence among HIV-infected adolescents. The second study included only a small sample of HIV-infected adolescents. To our knowledge, this study is the first comprehensive investigation of barriers to antiretroviral adherence among this population, and the first study among adolescents or adults to investigate the factor structure of the most commonly used antiretroviral barriers to adherence scale.28 Two major factors from the barriers scale were found: physical and psychological medication-related adverse effects, and problems in daily routines. The results of this study, indicating the most common adherence barriers among HIV-infected adolescents, have implications for medication adherence interventions for this group. Finally, this study provides the initial factor analysis structure of the barriers scale, which will allow other investigators to determine if these findings are replicable across other samples and other HIV-infected patient populations.

to-day routines. Unfortunately, this suggests that a broad spectrum of issues—from adverse effects, to not wanting to be reminded that one is HIV infected, to being busy with other life issues—are all adversely affecting HIV-infected adolescents’ antiretroviral medication adherence. Adherence interventions developed for adolescents need to be considered when designing behavioral change programs.

CONCLUSIONS

Human immunodeficiency virus–infected adolescents in this sample showed poor antiretroviral regimen adherence. Given this, it is likely over time that in treating adolescents, physicians will most likely follow the federal Health and Human Services guidelines regarding delaying or deferring therapy as much as possible. While the goal of treatment with fewer, simpler drug regimens, or with structured intermittent therapies, is an important one, particularly for adolescents, there will always be a need to maximize adherence to a given therapeutic regimen regardless of what the specifics of a given regimen might be. A major challenge facing HIV-infected adolescents is to be able to maintain full adherence to complicated medication regimens over long periods and perhaps for their entire lifetime. Patient-level intervention, health care provider–level intervention, and health care system modification may all be necessary if this challenge is to be met successfully, and interventions to assist these adolescents in improving adherence are urgently needed.

The following investigators, listed in order of the numbers of subjects enrolled, are participating in this study: University of Miami, Miami, Fla: Lawrence Friedman, MD; Lorraine Pall; Donna Maturo; Ann Pasquale. Montefiore Medical Center, The Bronx, NY: Donna Futterman, MD; Dina Monte; Maria Alovera-DeBellas; Neal Hoffman; Stacey Jackson. University of Pennsylvania and the Children’s Hospital of Philadelphia: Don Schwarz, MD; Bret Rudy, MD. Children’s Hospital of Philadelphia: Mary Tanney, MSN; Andrea Feldman. Children’s Hospital of Los Angeles, Los Angeles, Calif: Marvin Belzer, MD; Diane Tucker; Chris Hosmer, MSN; Katie Chung, MSN. Tulane Medical Center, New Orleans, La: Sue Ellen Abdalian, MD; Leslie Green; Chi McKendall; Luann Wenthold. Children’s National Medical Center, Washington, DC: Lawrence J. D’Angelo, MD; Connie Trexler; Carleen Townsend-Akpan; Rita Hagler; Julia A. Morrissey, MSW. University of Maryland, Baltimore: Ligia Peralta, MD; Celia Ryder, MSN; Sue Miller; Susan Calianno. Cook County Hospital/University of Chicago, Chicago, Ill: Lisa Henry-Reid, MD; Rosa Camacho. Children’s Hospital, Birmingham, Ala: Marsha Surdevant, MD; Allie Howell; Julie E. Johnson. Children’s Diagnostic and Treatment Center, Fort Lauderdale, Fla: Ana Puga, MD; Deanna Cruz; Patricia McLendon. Emory University, Atlanta, Ga: Mary Sawyer, MD; Jennifer Tigner; Ann Simmonds. St Jude Children’s Research Hospital, Memphis, Tenn: Patricia Flynn, MD; Kim Lott; Jennifer Dewey; Sally Discenza. Mount Sinai Medical Center, New York, NY: Linda Levin, MD; Mary Geiger. University of Medicine and Dentistry of New Jersey, Newark: Paulette Stanford, MD; Felecia Briggs, MS. SUNY Health Science Center at Brooklyn, Brooklyn, NY: Jeffrey Birnbaum, MD; Moham Ramnarine, MD; Vera Guarino.

The following investigators have been responsible for the basic science agenda: Center for Virology, Immunology, and Infectious Disease, Children’s Research Institute. Children’s National Medical Center: Christie Holland, PhD. University of California at San Francisco: Anna-Barbara Moscicki, MD. University of California at Los Angeles: Debra A. Murphy, PhD. University of Alabama at Birmingham: Sten H. Vermund, MD, PhD. The Fearing Laboratory, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass: Peggy Crowley-Nowick, PhD. University of Pennsylvania and the Children’s Hospital of Philadelphia: Steven D. Douglas, MD.

Network operations and analytic support are provided by the following: University of Alabama at Birmingham: Craig M. Wilson, MD; Cindy Partlow, MEd. Westat, Inc, Rockville, Md: Stephen J. Durako; Jonas H. Ellenberg, PhD; Brigid Hobbs; Ann Bennett; Margaret Camarca, MPH; Kathy Clingan; Jolene Houser; Viju Junankar; Olga Leytush; Larry Muenz, PhD; Yong Ma, MS; Rick Mitchell; Thuzar Myint, MS; Pete Ohan; Laura Paolinelli, MSN; Manisha Rakheja, MS; Moussa Sarr, MD, MPH; Anna Soloviov, MS.

Staff from sponsoring agencies include the following: National Institute of Child Health and Human Development, Washington: Audrey Rogers, PhD, MPH; Anne Willoughby. National Institute of Drug Abuse, Bethesda, Md: Katherine Davenny, MPH; Vince Smeriglio, PhD. National Institute of Allergy and Infectious Diseases, Bethesda: Elaine Matzen. National Institute of Mental Health, Bethesda: Ben Vitiello, MD.
Accepted for publication September 20, 2002.

This study was supported by grant U01 HD32827 from the National Institute of Child Health and Human Development, Bethesda, Md, given to the Adolescent Medicine HIV/AIDS Research Network, with supplemental funding from the National Institutes on Drug Abuse, Allergy, and Infectious Diseases, and the Mental Health and the Health Resources and Services Administration.

We are grateful to the members of the Community Advisory Board for their insight and counsel and particularly indebted to the youth who are making this study happen.

Corresponding author and reprints: Debra A. Murphy, PhD, Health Risk Reduction Projects, Department of Psychiatry, University of California, Los Angeles, 11075 Santa Monica Blvd, Suite 200, Los Angeles, CA 90025-3556 (e-mail: dmurphy@mednet.ucla.edu).

REFERENCES